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Shear Wave Velocity Measurements of the Brachial Artery in a Population with End-Stage Renal Disease

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1 Abstract

Introduction: Arterial elasticity measurements have been suggested as a possible biomarker for arterio-venous fistula failure. Elasticity can be non-invasively measured through ultrasonic induction of a shear-wave in tissue. The velocity of this wave is proportional to the square root of Young's Modulus. This pilot study sought to assess an imaging protocol to measure elasticity in the brachial artery via shear wave elastography (SWE) and determine if differences in shear wave velocity could be observed between a healthy group, and a group with end-stage renal disease (ESRD). Methods: 40 healthy volunteers were recruited into this study. All participants underwent US assessment of brachial artery elasticity via SWE. Brachial artery SWE images of 47 patients with ESRD were retrospectively analysed for comparison. Results: Brachial artery shear wave velocity was measured from each image. The imaging protocol was possible in all volunteers. The mean shear wave velocity was significantly lower in the patient group (3.2 $\pm$ 0.5 m/s in patients; 3.4 $\pm$ 0.4 m/s in

volunteers, P <0.05). Conclusion: The results from this pilot study suggest SWE measurements of brachial artery mechanics are feasible and can quantify arterial alterations possibly associated with ESRD. SWE may find use in the pre-operative assessment for patients awaiting arterio-venous fistula creation.

2 Introduction

End Stage Renal Disease is a progressive disease, that ultimately leads to the loss of kidney function. Patients with severe end stage renal disease require renal replacement therapy, commonly occuring via haemodialysis. Adequate haemodialysis requires filtration of the blood, at a high flow rate. Usually this is upwards of 400ml/min and requires a dedicated vascular access. The Arterio Venous Fistula (AVF) revolutionised vascular access by allowing repeated access to a high blood flow, through the surgical anastomosis between an artery and a vein [1]. Following creation of the AVF, blood flow through the vessels increases, with the artery and vein dilating in response [2, 3]. After around 6-weeks, the AVF should have developed a high enough flow in the venous segment to support haemodialysis.

AVFs suffer from high primary failure rates of around 30-40% after 1 year [4, 5]. In a bid to reduce failure, pre-operative ultrasound (US) mapping is performed, which commonly consists of searching for stenosis or calcification and assessing vessel diameters. However, there is little agreement on a vessel diameter cut-off for AVF creation [6, 7, 8]. Pre-operative US has shown the ability to increase AVF placement and decrease immediate failure rates, but meta-analysis has not shown any long term benefit [9, 10] in reducing failure rates. Identifying additional US based markers of AVF dysfunction may aid in increasing long-term primary patency, as current US practice has not.

Arterial stiffness has recently been proposed as a possible biomarker for AVF failure [11] by possibly inhibiting arterial dilation. Kheda *et al* [12] demonstrated that AVFs that failed to mature had a lower small artery elasticity index than those which reached a state useable for haemodialysis. If the artery cannot dilate, it is hypothesised that the AVF conduit cannot produce the flow rates which stimulate venous dilation, and suitable for haemodialysis.

Assessing arterial stiffness relies on the physics of waves, and the phenomenon that stiffer arteries will propagate a faster pulse wave. The speed of the pulse, the pulse wave velocity, can be measured between two sites a known distance apart using tonometers. Commonly the measurement is made between the carotid, and a more distal point such as the radial or femoral arteries. Pulse wave velocity can be expressed in terms of Young's Modulus, and increases with its square root. However, this type of measurement masks over regional changes in elasticity, and often inaccurate path lengths are a problem.

Local measurement of tissue stiffness is possible. Advances in Ultrasound (US) technology have lead to the possibility of sonographically mapping tissue stiffness. Shear wave elastography, pioneered by Fink *et al* [13], uses shear waves generated from focussed US to map tissue stiffness. A shear wave causes particles in a medium to oscillate in a transverse direction to the wave motion. The wave propagation velocity is related to Young's Modulus:

$$Young's\ Modulus = 3 \times density \times (shear\ wave\ velocity)^2 \tag{1}$$

This equation relies on various mechanical assumptions, such as elastically homogenous materials, infinite in space, which are biologically unrealistic [14]. By tracking the motion of these waves through a tissue sample using high frame-rate techniques it is possible to estimate the velocity, and obtain an indirect measurement of tissue stiffness.

Shear wave elastography has found widespread clinical application in breast, liver, thyroid and lymph node imaging [15, 16, 17, 18]. Recently, a number of studies have used shear wave elastography to investigate the cardiovascular system [19, 20], including identifying increased elastic modulus in the carotid in a group with ischemic stroke [21]. It is possible that shear wave elastography techniques could differentiate between vessels which mature into successful AVFs, and those which do not. In doing so, it may aid in the selection of more suitable vessels for AVF creation, or help better the counseling of

patients in regards to the risk of AVF failure.

Brachial artery shear wave elastography measurements are currently being trialled as part of the pre-operative assessment for AVF creation in our institution. We wished to assess the difference in brachial artery elasticity in patients awaiting AVF creation and with a healthy group recruited locally in order to determine baseline shear-wave velocity measurements to be used as a reference for future studies, and to determine if any disease or age related effect could be observed.

3 Materials and Methods

3.1 Study Population

Patient data was collected retrospectively from vascular laboratory databases, on patients who had undergone a pre-operative assessment for AVF creation for haemodialysis. Healthy volunteers were recruited locally, and informed consent was obtained. The study received ethical approval from the East Scotland Research and Ethics Council. Caldicott Approval was granted to obtain retrospective patient data The authors have confirmed that any identifiable participants in this study have given their consent for publication.

3.2 US Scanning

Healthy volunteers underwent US scanning which was identical to part of the pre-operative scan for patients. All scans were performed on a Siemens S2000 Ultrasound machine (Siemens, Germany) with cardiovascular modules installed and a 9 MHz linear probe. Three ECG patches were placed on the participant and connected to the US machine. Participants were seated facing the operator and the arm of interest extended over a pillow as in Fig. 1. The arm was extended from the chest to avoid breathing motion.

Figure 1: Participant positioning for US scanning

The US probe was used to locate a straight segment of the brachial artery proximal to the cubital fossa in a transverse view. The probe was then rotated through 90 degrees to obtain a longitudinal view of the brachial artery. A clear view of the intima layer of the artery was desired. Vessel walls parallel to the scanner probe axis were prioritised over non-parallel regions to avoid errors in shear wave velocity estimation.

The shear wave elastography function (Virtual Touch IQ) was selected on the machine, and a rectangular shaped region of interest (ROI) was placed over the vessel wall. Upon user input, a shear wave was generated and then displayed as a velocity map superimposed over the B-Mode image. 8 square shaped ROIs were placed along the vessel wall enclosing the intima as in Fig. 2, avoiding any areas of noise. All images were stored on the hard-drive of the US machine for analysis.

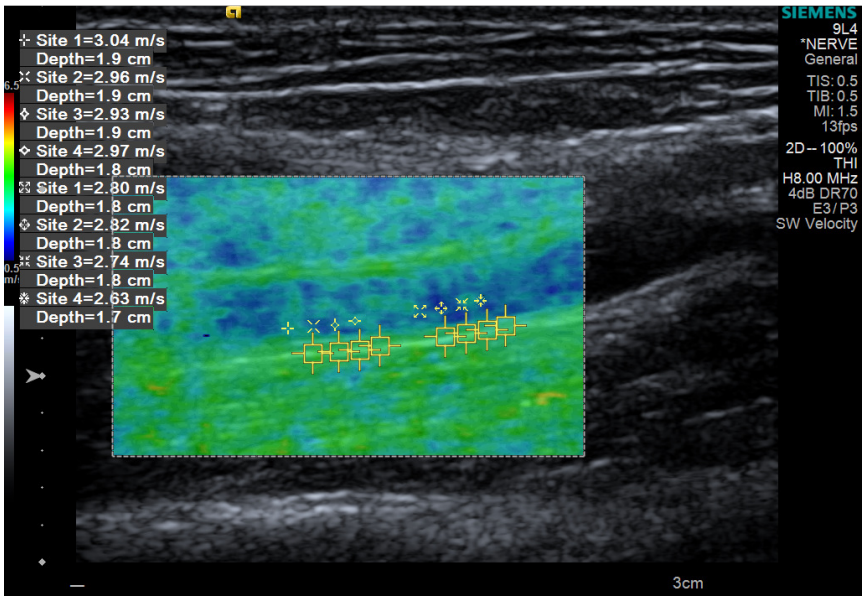
A number of volunteers were selected at random to undergo assessment of both the left and right arm, in order to determine if shear wave velocity measurements were similar for both arms. Results from the two arms were compared using a Wilcoxon signed-rank test, used to compare two related samples, allowing determination if the two samples were taken from populations having the same distribution.

3.3 Statistical Analysis

All data analysis was performed using Python 2.7 using the 'Matplotlib', 'Seaborn' and 'SciPy' packages. All data were collated as mean $\pm$ standard deviation. The standard deviation of each measurement was also stored as a separate variable, in order to assess the heterogeneity of the measurement.

Data was assessed for normal distribution graphically. Differences in mean variable values between the patient and volunteer groups were assessed using Student's T-test or a non-parametric equivalent if necessary. Correlations between variables were assessed

Figure 2: ROI placement along the brachial artery wall, fully enclosing the intima layer. This segment was not completely parallel to the transducer surface, resulting in varying depth of measurement points. Mean shear wave velocity is 2.9 ± 0.1 m/s.



using Pearson's r statistic. Data was also presented after normalisation, using min-max normalisation for a variable x and normalised value x′:

$$x' = \frac{x - min(x)}{max(x) - min(x)} \tag{2}$$

3.4 Inter-Operator Reproducibility

A number of volunteers were selected at random to undergo an additional identical assessment by a second US operator. The second operator was blinded to the exact location of previous scanning, and the results obtained. The correlation between the two operators was assessed using Pearson's r statistic, and displayed graphically with a regression line.

4 Results

40 healthy volunteers were recruited into this study. Shear wave elastography maps were obtainable for 47 patients. The mean age and BMI of the patient group was significantly higher than the volunteer group (both p <0.05). Participant demographics can be seen in table 1.

Table 1: Study participant demographics

Measurement	Patient (n = 47)	Volunteer (n = 40)	P-value
Age (years)	66 ± 13	36 ± 15	**<0.05**
Male (%)	55	45	0.33
BMI ($kg\ m^{-2}$)	29 ± 6	23 ± 6	**<0.05**
Diabetes (%)	38	0	-
Hypertension (%)	77	0	-

Mean shear wave velocity measurements can be viewed in table 2, including normalised values of the shear wave velocity measurements. Significant differences were seen between the shear wave velocity for the patient and volunteer group, with the volunteer group showing velocity values that were 6.3 % larger. These results are displayed graphically in Fig. 3. The average standard deviation in the shear wave velocity measurement was similar between the two groups, suggesting the shear wave velocity measurements were similarly homogenous. A significant negative association between age and shear wave velocity was observed (r = -0.2, p = 0.05), a scatter plot with a regression line fitted can be seen in Fig. 4. In 20 patients, no significant difference was observed between the left and right arm using a Wilcoxon ranked test (statistic = 95, p = 0.70).

A random selection of 15 patients underwent shear wave velocity scanning by an additional operator, blinded to results of the first assessment. Strong agreement was observed between the two operators when assessed using Pearson's r statistic (r = 0.92, $p = 1 \times 10^{-6}$), a scatter plot with a regression line fitted can be seen in Fig. 5.

Figure 3: Boxplots of shear wave velocity values for patients and volunteers, horizontal lines inside the coloured boxes indicate median values

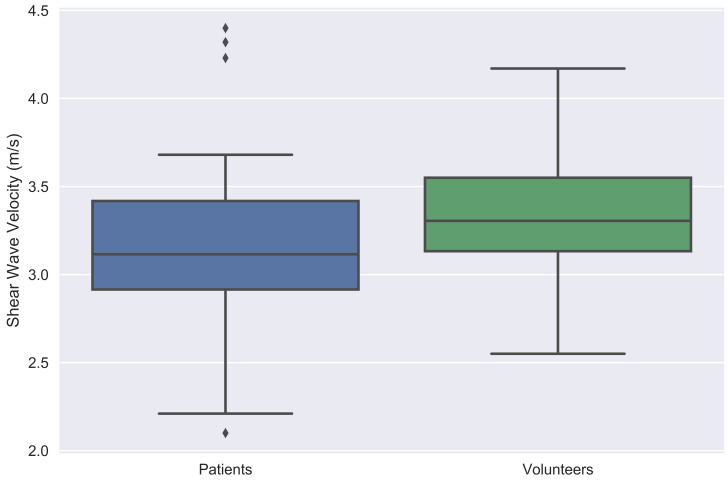


Figure 4: Scatter plot of age and shear wave velocity measurements for both patients and volunteers, with a regression line fitted. Vertical lines for each marker represent the standard deviation of a single measurement. A significant negative association is observed, pearson's r = -0.2, p = 0.05

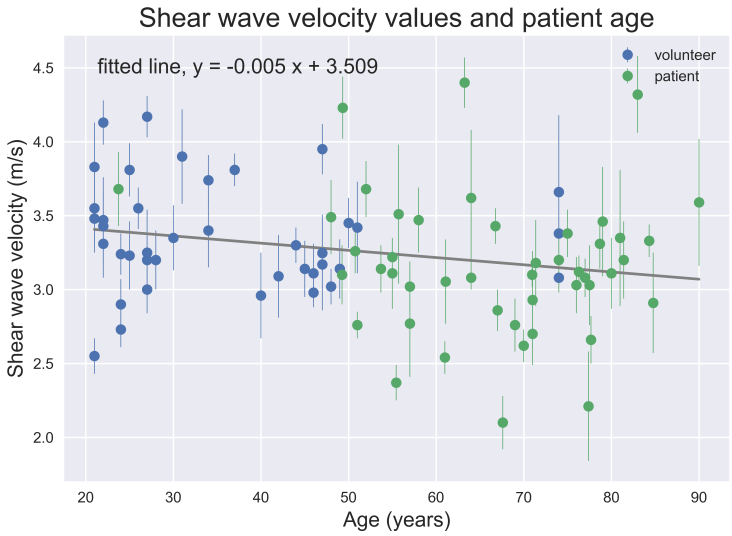


Figure 5: Scatter plot of shear wave velocity measurements from two operators, with a regression line fitted. Vertical lines for each marker represent the standard deviation of a single measurement. Strong significant correlation is observed, pearson's r = 0.92, p = 1×10^{-6}

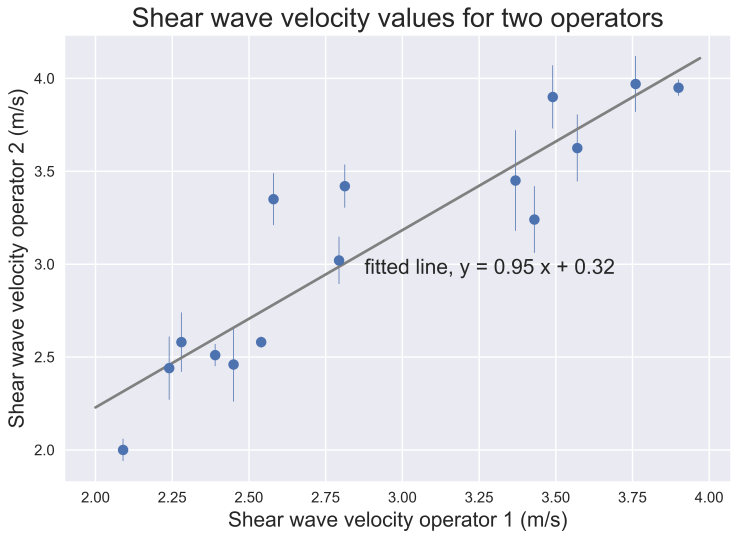


Table 2: Mean SWE measurements between for the two groups, the standard deviation in the mean for each individual shear wave velocity mean measurement was stored as a separate variable, in order to assess the homogeneity; s.d. standard deviation

Measurement	Patient (n = 47)	Volunteer (n = 40)	P-value
Shear Wave Velocity (ms^{-1})	3.2 ± 0.5	3.4 ± 0.4	**0.03**
Normalised Shear Wave Velocity	0.46 ± 0.2	0.54 ± 0.15	-
Shear Wave Velocity s.d. (ms^{-1})	0.2 ± 0.1	0.2 ± 0.1	0.40

5 Discussion

This study aimed to assess if differences in shear wave elastography measurements of the brachial artery existed between a healthy group, and a group with end-stage renal disease. These results confirm that shear wave velocity measurements of the brachial artery are possible using the shear wave elastography method in a cohort of 87 individuals. We have observed a negative correlation with age, indicating that the brachial artery becomes less stiff with age.

Shear wave elastography measurements were simple, repeatable, and no specialist equipment was needed, as is the case for pulse wave velocity measurements, except the widely available software on the US machine. The high inter-operator reproducibility between two operators with different experience demonstrates the suitability of this technique for vascular assessments. Volunteers were imaged seated, in a position which was comfortable and bearable. This protocol can be easily implemented onto the pre-operative assessment before a patient has an AVF placed, and may provide additional clinical information.

Shear wave velocity in the brachial artery of the healthy group was higher than in the patient group. As the velocity is related to the square root of Young's Modulus, these results indicate that the brachial artery of an elderly group of patients with end-stage renal disease is more compliant than that of the healthy volunteers. Patients with end-stage renal disease are known to have increased arterial stiffness, although previous studies have found that the brachial artery compliance may not decrease with age [22, 23, 24]. Different trends in carotid and aortic stiffness have been observed in patients with chronic kidney disease [25], and it is possible that similar phenomena are being seen in the brachial artery.

The difference in age and BMI between the two groups is a limitation in this study. We observed a significant negative correlation with age and shear wave velocity measurement in the whole group (n = 87). As the groups are not age matched, we cannot determine if

the observed difference in shear wave velocity is due to age or disease related changes. The patient group had a mean age of 66 ± 13 years, making it hard to match with a disease-free group.

This study did not compare shear wave elastography measurements with another modality, such as pulse wave velocity. We therefore cannot determine if shear wave elastography can provide measurements of global arterial stiffness, as pulse wave velocity can. Future work can compare the modalities in other vessels such as the carotid for correlation, in order to determine if shear wave elastography can act as a simple US based marker of arterial stiffness. The ease of imaging makes this an attractive method if such a correlation were to be found. It should be noted however, that shear wave velocity measurements may vary between manufacturers. For this reason it may be more appropriate to consider normalised differences in shear wave velocity values between groups, as we have included in the results.

To minimise errors, vessel walls parallel to the US transducer surface were desired. In a number of patients, this was not straight-forward. Therefore, the shear wave elastography method is limited by a number of technical factors, mainly age and BMI. It was observed that some elderly participants showed arteries much more tortuous than younger participants. For some participants within this group, it was difficult to find a suitable region of artery close to the cubital fossa, that was parallel to the transducer surface. High BMI resulted in shear wave velocity measurements taken at a greater depth than in patients within the healthy BMI range. In younger participants with a healthy BMI, a suitable patch of artery for shear wave velocity measurements was commonly found just proximal to the cubital fossa.

On our machine (Siemens S2000), it was not possible to gate the shear wave velocity measurements with the cardiac cycle. This is a limitation of the current technique, as one

study in a single volunteer has shown that shear wave velocity measurements in the carotid vary throughout the cardiac cycle [19]. This limitation is noted in other vascular studies of shear wave velocity [20, 21]. However, the strong inter-operator agreement, and lack of difference between arms suggests that if there is some time dependent effect on these measurements, the effect is too small to introduce a significant error in the results.

The patient participants in this study were all listed for AVF creation, and will be followed for a period of 6-months after the AVF has been created, in order to determine which values of shear wave velocity can be used to predict AVF-risk. Now that baseline values, and an age correlation have been observed, future work will aim to determine if differences exist in patients with a successful AVF and patients whose AVF failed to support dialysis. We hypothesise that higher stiffness in the brachial artery may hinder dilation, resulting in a flow which may be too low to support haemodialysis.

6 Conclusion

In conclusion we have demonstrated that shear wave elastography can quantify differences in brachial artery stiffness in two groups. We have observed that the brachial artery in elderly patients with end-stage renal disease permit slower propagation of shear waves than in a healthy younger group, suggesting more elastic vessels. This imaging protocol may be easily extended to other blood vessels in other trials, and can form part of the pre-operative assessment for AVF creation in patients with end-stage renal disease.

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